REMARKS

Claims 1, 2, 4-24, 27 and 34-38 are currently pending in the present application. Claims 9-24 have been withdrawn from consideration.

With respect to the previous claim amendments and the Examiner's comments relating thereto in the Advisory Action, Applicants respectfully submit that the claim amendments are consistent with the elected and examined species. That is, the elected species of B and T cells are present in claims 1 and 2. Moreover, the elected species of IgG is present in claims 6 and 36. The previous claim amendments do not serve to broaden the scope of the examined claims as alleged by the Examiner in the Advisory Action. Rather, Applicants are only correcting the genotypic designation as pointed out by the Examiner in "Claim Objections" discussed below. The elected species is still present and recited in claims 8 and 38.

Accordingly, Applicants respectfully request entry and consideration of the claim amendments filed in the Response dated April 13, 2009.

Claim Objections

Claims 1, 2, 4-8 and 34-37 stand objected to. In the Office Action, the Examiner states that the NOD/SCID genotypic designation is reserved for mice and is not generally applicable to other mammals. Thus, the claims should be amended to recite a NOD/SCID/IL2rg-null mouse.

In response to the Examiner's objection, claims 1, 2, 4-8, 34-38 have been amended to replace "NOD/SCID/IL2rg-null mammal" with "SCID/IL2rg-null mammal". "NOD/SCID" is one of the "SCID", which is described in the specification (e.g., page 7, line 20 – page 8, line 3 of the present specification). The term "NOD" is used specifically for mice. However, "SCID" is generically applicable to mammals (i.e., rats, rabbits, dogs, pigs and mice).

On page 2 of the Advisory Action, the Examiner has taken the position that the amendments presented in the last response are considered to be new matter. In the last response directed the Examiner's attention to page 7, line 20 – page 8, line 3 of the present specification as support for the claim amendments. Thus, Applicants are unsure why the Examiner is of the opinion that the claim amendments introduce new matter.

For the Examiner's convenience, the relevant portion of the specification at page 7, lines 8-25, recites:

> Immature immunodeficient mammal
>
> ***In the present invention, animals used as recipients, into which human-derived hematopoietic precursor cells are transplanted, are immunodeficient mammals other than humans. The term "immature mammal" is used in the present invention to mean mammals including the stages ranging from a fetus and a newborn, up to an individual with a reproductive age.*** It is preferably a fetus and a newborn baby with an age of 7 days or less, and more preferably a newborn baby with an age of 2 days or less. When an immature immunodeficient mammal is used as a recipient, human immunocompetent cells efficiently proliferate as such an individual grows up. Thus, it is preferable to use such an immature individual in the present invention.
>
> ***Examples of a mammal may include a mouse, a rat, a hamster, a guinea pig, a sheep, a miniature pig, a pig, and a monkey. Immunodeficient mice are preferable in that there have been many types of model animals and in that the strains thereof have already been established. The term "immunodeficient mouse" is used to mean a severe combined immunodeficiency disease mouse (SCID mouse) that lacks ability to produce T cells and B cells.*** In particular, an NOD/SCID/β2 microglobulin knockout mouse (NOD/SCID/B2M) and an NOD/SCID/common γ-chain knockout mouse, which do not have the activity of NK cells, are preferable.

Thus, from the above passage, while it is clear that the mouse model is preferred, the immunodeficient mammal of the present invention is not limited to mice, and may include other mammals.

Further, Applicants respectfully submit that, at the very least, the present specification also provides implicit support for the claim amendments. In accordance with MPEP § 2163, "there is no *in haec verba* requirement, . . . claim limitations must be supported in the specification through express, implicit, or inherent disclosure."

As the Examiner pointed out in the Office Action dated January 13, 2009, "it should be noted that the NOD/SCID genotypic designation is reserved for mice, and is not generally applicable to other mammals." Thus, it is apparent from the specification that many different types of mammals, excluding humans, were contemplated by Applicants. Mice are merely noted as being preferable. Amending the claims in the previous manner was done to address the Examiner's concerns regarding what is known in the art, and did not necessarily require limiting the claims to NOD/SCID/IL2rg-null mouse as suggested by the Examiner.

Accordingly, reconsideration and withdrawal of the outstanding objection are respectfully requested.

Rejections under 35 U.S.C. §103(a)

Claims 1, 2, 4, 5, 8, 34, 35 and 38 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by Ishikawa et al. (Exp. Hematol. 30(5):488-494; May 2002) (hereinafter "Ishikawa") in view of mouse strain NOD.Cg-*Prkdc*^{scid} IL2rg^{tm1Wjl}/Sz (Stock No.:005557, Jackson Laboratory) (hereinafter "Stock No. 005557").

However, Applicants respectfully submit that it would not have been obvious for a person of ordinary skill in the art to combine the teachings of Ishikawa and Stock No. 005557 to arrive at the presently claimed invention for the following reasons.

In the present response, claims 1 and 2 have been amended to recite "wherein the immunocompetent cells comprise B cells, T cells and dendritic cells". The present specification teaches that a newborn SCID/IL2rg-null mammal of the present invention is able to generate all of B cells, T cells, and dendritic cells derived from the human-derived hematopoietic stem or precursor cells. *See* the present specification, Example 7, at page 26, lines 4-11; and page 28 line 3 – page 30, line 2.

Example 7 demonstrates that engrafted human-derived hematopoietic stem or precursor cells in a newborn SCID/IL2rg-null mammal are able to differentiate consistently and efficiently into mature B cells, T cells and dendritic cells. Further, these mature B cells, T cells and dendritic cells are functionally-differentiated cells from the human-derived hematopoietic stem or precursor cells so that they can cooperatively induce antigen-specific immune response, e.g., generation of antigen-specific human immunoglobulin. *See* the present specification, Example 9, page 31, line 7 – page 32, line 12. Moreover, full representation of phenotypically and functionally mature human immune subsets enable Applicants to investigate homeostasis and dynamics of human hematopoietic and immune systems *in vivo*.

In contrast, Ishikawa and Stock No. 005557 do not teach or suggest that a newborn SCID/IL2rg-null mammal into which human-derived hematopoietic stem or precursor cells have been transplanted is able to generate all of B cells, T cells, and dendritic cells derived from the human-derived hematopoietic stem or precursor cells.

In addition, Ishikawa and Stock No. 005557 do not teach or suggest that engrafted human-derived hematopoietic stem or precursor cells in a newborn SCID/IL2rg-null mammal are able to differentiate into mature B cells, T cells and dendritic cells.

Many factors are needed for the differentiation of engrafted human-derived hematopoietic stem or precursor cells into immunocompetent cells in heterologous mammals. According to conventional means, it is uncertain whether the engrafted hematopoietic stem cells

or precursor cells are able to functionally differentiate into B cells, T cells and dendritic cells in heterologous mammal. However, the present invention alleviates the previous unpredictability of this process. That is, the present invention efficiently and consistently takes engrafted human-derived hematopoietic stem or precursor cells in a newborn SCID/IL2rg-null mammal, and differentiates them into mature B cells, T cells and dendritic cells.

Therefore, even if a person of ordinary skill in the art would combine the disclosures of Ishikawa and Stock No. 005557, as suggested by the Examiner, it would not have been obvious to arrive at the mammal of the present invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

Claims 1, 2, 6, 7, 36 and 37 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by Ishikawa in view of Stock No. 005557 and further in view of Olive et al., (Immunol. Cell Biol. 76:520-525, 1998) (hereinafter "Olive").

However, Applicants respectfully submit that it would not have been obvious for a person of ordinary skill in the art to combine the teachings of Ishikawa, Stock No. 005557 and Olive to arrive at the presently claimed invention.

In the present response, claims 6 and 36 have been amended to recite "wherein the immunoglobulin comprises IgG, IgM, IgA and IgD". The present specification teaches that a newborn SCID/IL2rg-null mammal ("the claimed mamamal") is able to generate all of IgG, IgM, IgA and IgD. These immunoglobulin are derived from the immunocompetent cells comprising B cells, T cells and dendritic cells derived from the human-derived hematopoietic stem or precursor cells. *See* the present specification, Example 7, especially, page 26, line 15 – page 27, line 8; and Fig. 7. Particularly, the present specification teaches that generation of human IgG and IgM in

the claimed mammal is highly efficient. *See* the present specification, page 27, lines 15-18; and Table 3. In addition, Example 8 shows that human IgA was generated in the intestinal villi of the claimed mammal. *See* the present specification, page 30, lines 15-26; and Fig. 10. Moreover, IgG, IgM, IgA and IgD can be antigen-specific. *See* the present specification, Example 9, page 31, line 7 – page 32, line 12.

In contrast, Ishikawa, Stock No. 005557 and Olive do not teach or suggest that a newborn SCID/IL2rg-null mammal into which human derived hematopoietic stem or precursor cells have been transplanted is able to generate human IgG, IgM, IgA and IgD; which are derived from the immunocompetent cells comprising B cells, T cells and dendritic cells derived from the human-derived hematopoietic stem or precursor cells. Generation of human IgM, IgA, and IgD are not taught or suggested by Ishikawa, Stock No. 005557 and Olive.

Many factors and differentiation of various immunocompetent cells and immune tissues are required to generate human IgG, IgM, IgA and IgD in heterologous mammals. According to conventional means, it is unclear whether the engrafted human-derived hematopoietic stem cells or precursor cells can differentiate into various human immunocompetent cells or tissues in heterologous mammals. It is also unclear from conventional methods whether various kinds of immunoglobulin are generated.

The present invention alleviates the previous unpredictability of the conventional prior art. According to the present invention, engrafted human-derived hematopoietic stem or precursor cells in a newborn SCIDIIL2rg-null mammal differentiate into human immunocompetent cells, and the mammal is able to generate all of human IgG, IgM, IgA and IgD derived from the human immunocompetent cells. Further, the IgG, IgM, IgA and IgD of the present invention are antigen-specific.

Therefore, even if a person of ordinary skill in the art combines the teachings of Ishikawa, stock no. 005557 and Olive, it would not have been obvious for a person of ordinary skill in the art to arrive at the mammal of the presently claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

In view of the foregoing, Applicants believe the pending application is in condition for allowance. A Notice of Allowance is earnestly solicited.

CONCLUSION

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Monique T. Cole, Reg. No. 60,154 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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